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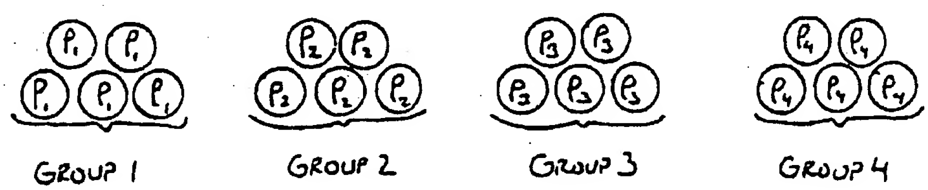

(57) Abstract

The invention provides an exemplary chemical library which includes a plurality of constructs which are separable into physically distinct groups. The constructs in each group have at least one common physical characteristic, which is physically distinct from the physical characteristics of the constructs in all other groups. The physical characteristics represent the manner by which the group is testable. The constructs are especially bead–linker–tag–ligand systems. The physical characteristics are especially the size or density of the bead. Preferably, the physical characteristic of a bead is indicative of the type of linker used, which provides easy recognition of constructs suitable for use in specific assays.

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ENCODING SCHEME FOR SOLID PHASE CHEMICAL LIBRARIES

BACKGROUND OF THE INVENTION

The invention relates generally to the field of combinatorial chemistry, and in particular to encoding schemes for solid phase chemical libraries. More specifically, the invention relates to the production of constructs which have different physical characteristics to allow the constructs to be physically separated into different groups.

Recent trends in the area of research for novel chemical and especially pharmacological agents have been concentrated on the preparation of so-called "chemical libraries" as potential sources of new leads for drug discovery. Chemical libraries are intentionally created collections of differing molecules which can be prepared either synthetically or biosynthetically and screened for biological activity in a variety of formats. Examples of chemical libraries include libraries of soluble molecules; libraries of compounds tethered to resin beads, silica chips or other solid supports; or recombinant peptide libraries displayed on bacteriaphage or other biological display vectors.

Of particular interest to the present invention are chemical libraries which are tethered to individual solid supports, which typically take the form of resin beads. A variety of techniques have been proposed for making chemical libraries which utilize individual solid supports to which the compounds are tethered. One such method is the "discrete" method where solid supports are placed into multiple reaction vessels. Various chemicals are then synthesized onto the solid supports while the solid supports remain within the reaction vessels. After completing the synthesis process, the chemical compound on each solid support may be identified simply by identifying the reaction vessel from which the solid support was removed. Because of the need to maintain the solid supports within a given reaction vessel, the size of the resulting chemical library is limited by the number of reaction vessels used.

In an attempt to greatly increase the size of a chemical library, the mix and split technique was developed. In the mix and split method, solid supports are placed into individual reaction vessels and a first building block is synthesized onto each of the solid supports. Solid supports are then mixed together and redistributed to the reaction vessels where a second building block is synthesized onto the solid supports. The solid supports may once again be mixed and redistributed where another building block may be synthesized onto the solid supports. This process may be repeated as many times as necessary. Examples of mix and split techniques are described generally in U.S. Patent No. 5,503,805, the complete disclosure of which is herein incorporated by reference.

As an example of split synthesis in the solid state synthesis of peptides, a batch of resin supports (typically small resin beads) may be divided into n fractions, coupling a single monomer amino acid to each aliquot in a separate reaction, and then thoroughly mixing all of the resin particles together. Repeating this protocol for a total of x cycles can produce a stochastic collection of up toeometric distribution. Further, to ensure representation of the majority of possible ligan n^x different molecules, as governed by a hypergds, a relatively large number of beads should be employed. A typical value may be about ten times as many beads as the desired number of ligands.

Once a mix and split chemical library has been produced, the compound may be cleaved from the solid supports and tested to determine if the compound produces the desired result. If so, the particular compound needs to be identified. However, since the solid support was mixed and split one or more times during the synthesis process, identifying the compound on the solid support can be challenging.

As described in greater detail thereafter, some have proposed to associate labels with the compounds as they are proceeding through their combinatorial steps. For example, where the compounds are tethered to resin beads, prior art solutions to the problem have included attaching chemical identifier tags to the beads coincident with each block coupling step in the synthesis. The determined

properties of each tag then convey which building block was coupled in a particular step of the synthesis. The overall structure of a ligand on any bead may then be determined by reading the set of tags on that bead, in effect having encoded the bead.

An alternative method for producing combinatorial libraries of chemicals involves techniques utilized by both the discrete method and the mix and split method. According to this hybrid method, solid supports are placed at discrete locations and a set of chemicals are synthesized onto each of the solid supports while they remain within their discrete locations. A ligand code is also coupled to each of the solid supports, and may be used to identify the chemicals synthesized onto their solid supports while at their discrete locations. The solid supports are then mixed and split where still another chemical is synthesized onto each of the solid supports. The chemical compound on each of the solid supports may then be identified by knowing the position of the solid support when the last building block was added, and by reading the ligand code to determine the chemical compounds added while the solid supports were at their discrete locations. Such a technique is described generally in PCT International Application No. PCT/US97/05701, and in H. Mario Geysen, et al., Isotope or Mass Encoding of Combinatorial Libraries, *Chem. & Biol.* Vol. III, No. 8, pp. 679-688, August 1996, the complete disclosures of which are herein incorporated by reference.

As previously mentioned, because the solid supports are combined together and then redistributed into reaction vessels, there is a need to identify the components of the ligands as they are synthesized onto the solid supports. In this way, the chemical synthesis steps may be determined so that the final compound synthesized onto the solid supports may be determined. A variety of encoding schemes have been proposed to record the synthesis process. One such technique is the parallel encoding technique where the progressive assembly of tags is performed in conjunction with the construction of the ligand. The tags are used as a binary code to record the reaction history of each bead. The code can then be read directly from a single bead by electron capture capillary gas chromaphotography. Such a process is described generally in Michael H. J. Ohlmeyer, et al., Complex Synthetic Chemical

Libraries Indexed with Molecular Tags, *Proc. Natl. Acad. Sci. USA*, vol. 90, pp. 10922-10926, December 1993, the complete disclosure of which is herein incorporated by reference.

Another encoding strategy proposes the use of a microelectronic device called a radio frequency memory tag. This tag may be embedded into a solid support and provided with a unique binary code. To read the code, the chip is placed near a computer interface transceiver, which causes the chip to power up, read its identification tag, and send a code to the transceiver in an RF pulse. Such a technique is described generally in A. W. Czarnik, Encoding Strategies and Combinatorial Chemistry, *Proc. Natl. Acad. Sci. USA*, vol. 94, pp. 12738-12739, November 1997, the complete disclosure of which is herein incorporated by reference.

The complexity surrounding combinatorial libraries is often increased because of the requirement imposed by different chemists, which often prefer different types of assays in order to determine which ligands produce a positive result. For example, depending on the chemist, the combinatorial library may need to be compatible with direct binding assays, lawn assays, solution assays, and the like. As a result, multiple libraries may need to be produced, which each include the same set of ligands but which are constructed using a different process so that each of the libraries is conducive with a different type of assay. The use of different types of assays to evaluate chemical libraries is described generally in Daniolos, A. et al. *Pigment Cells Res.*, 3, 38-43 (1990); Jayawickreme, C. K., *Proc. Natl. Acad. Sci.* 91, 1614-1618; and Lam, Kit S., et al., "The 'One-Bead-One-Compound' Combinatorial Library Method", *Chem. Rev*, 1997, 97, 411-448, the complete disclosures of which are herein incorporated by reference.

As is readily apparent, the building of multiple libraries with identical ligands is both costly and time consuming. Hence, it would be desirable to provide ways to construct a single library that may be separated into groups such that each group is suitable for an appropriate assay format. More specifically, it would be desirable to provide a way to identify the manner of attachment of a linking component so that it may be determined which process may be employed to test the particular construct.

In one aspect, it would be desirable to provide additional ways to separate groups of constructs to increase the number of possibilities for identifying various aspects of the constructs.

SUMMARY OF THE INVENTION

The invention provides exemplary chemical libraries, methods for producing chemical libraries, and methods for evaluating chemical libraries. In one exemplary embodiment, a chemical library comprises a plurality of constructs which are separable into physically distinct groups. The constructs in each group have at least one common physical characteristic which is physically distinct from the physical characteristics of the constructs in all other groups. In this manner, the constructs may easily be separated into different groups based upon their common physical characteristics.

Examples of physical characteristics which may be utilized include size, density, geometry, color, magnetization, charge, refractive index, and the like, as well as those described in U.S. Patent No. 5,708,153, the disclosure of which is herein incorporated by reference. In one particular aspect, the physical characteristics are classifiable into categories. In this way, the category of at least one of the groups may be different from the other groups. As an example, one of the categories may be size and another one of the categories may be density. Hence, the chemical library may have constructs which have differing physical characteristics within the same type and/or physical characteristics of different types. In this way, the number of possibilities for different physical characteristics may be greatly increased.

In another particular aspect, each construct comprises a solid support to which are attached multiple components. Such components can include, for example, a ligand component and at least one linking component. In some cases, the construct may also include one or more one ligand coding components. Preferably, the constructs of each group have linking components which have been assembled in essentially the same manner. In this way, the common physical characteristic of each

group is representative of the process by which the group is testable, i.e., by knowing the manner of assembly of the linking components, one can determine the particular type of assay which should be employed to evaluate the ligand components. As such, the manner of assembly of the linking components of each group is preferably unique to each group. Once the constructs have been separated and tested, individual constructs which tested positive may be decoded (if appropriate) to determine the ligand.

In one particular aspect, the ligand component is composed of three different building blocks. Further, each ligand code component is readable to determine two of the building blocks on each solid support. In this way, the ligand code may be employed to determine the first two building blocks which were synthesized while the solid supports were placed at discrete locations. The solid supports may then be mixed and split where the third building block is synthesized onto the solid supports. As such, the third building block is known. Hence, the building blocks employed to produce the chemical composition may readily be determined by evaluating the ligand code component, while the manner of attaching the ligand components may be determined based on the physical characteristics of the construct.

The invention further provides an exemplary method for producing a chemical library. The method utilizes a plurality of solid support groups, where each group includes multiple solid supports which have at least one common physical characteristic which is different from the physical characteristics of the solid supports of the other groups. The method proceeds by attaching at least one linking component to each of the solid supports. The manner of attachment of the linking components is unique to each group as compared to the other groups. Further, a ligand is synthesized onto each solid support such that each group of solid supports receives the same ligands. In this way, a chemical library is produced where the manner of attachment of the linking components may readily be identified. Identification of the manner of attachment of the linking components is advantageous in that the process by which the group is testable to evaluate the ligand may be

determined simply by knowing the common physical characteristic of the group to which the solid support pertains. Optionally, one or more ligand coding components may also be attached. In such an event, a particular ligand may be identified by decoding the ligand component, typically after a tested construct has produced a positive result.

The physical characteristics by which the testable processes may be identified include size, geometry, density, color, magnetization, charge, refractive index, and the like. As previously described, the physical characteristics may be classifiable into categories so that the physical characteristics may differ within a given category or across certain categories. In one particular aspect, the processes by which the groups may be tested include direct binding assays, lawn assays, solution assays, and the like.

In one particular step, multiple solid supports are placed into physically discrete locations prior to the synthesizing step. Each of the locations is provided with at least one solid support from each of the groups. With this arrangement, one or more building blocks may be synthesized onto each solid support while the solid supports are at the discrete locations. With this arrangement, the ligand coding component is preferably representative of the building block(s). Following synthesis of the building block(s), the solid supports are preferably mixed and allocated into a plurality of vessels where another building block is synthesized on each of the solid supports. In this manner, the ligand may be identified by utilizing the ligand code to determine the initial building block(s). Further, the process by which each group is testable may be determined simply by determining the common physical characteristics of each of the groups. In this way, the solid supports may be separated into groups where each group is tested using a different assay. If a positive result is obtained, the ligand may be determined by reading the ligand code.

The invention further provides an exemplary method for evaluating a chemical library. According to the method, a plurality of constructs are provided which are typed by at least one common physical characteristic. The constructs have been separated into groups based on their type. Following separation, each of the

groups may be evaluated, with each group containing information which will assist in the evaluation process. For example, each group may require the performance of a different assay in order to evaluate the ligand. More specifically, the constructs of one group may have linking components which have been assembled in essentially the same manner so that the common physical characteristic of each group is representative of the process by which the group is testable.

In one particular aspect, the physical characteristic is density. In this way, the constructs may be separated by sequentially placing the constructs within fluids having different densities and removing the constructs that rise to the top of each fluid. As another example, at least one of the physical characteristics may be size. With this construction, the constructs may be sieved or agitated to permit the larger sized constructs to rise to the top of the remaining constructs. The larger size constructs may then be picked from the collection, preferably utilizing a picking device which can distinguish based on size.

In another embodiment, the invention provides an exemplary chemical library system which comprises at least two different chemical libraries. Each chemical library comprises a plurality of solid supports onto which at least two building blocks are coupled. The solid supports of each library have a unique physical characteristic common to the library which allows the library to which each solid support belongs to be identified. In this way, the libraries may be combined to facilitate testing. When desired, the library from which a particular solid support originated may be determined simply by evaluating its physical characteristic. The physical characteristics of the solid supports are preferably selected from a group consisting of size, geometry, density, color, magnetization, charge, and refractive index.

The invention further provides an exemplary method for evaluating two or more different chemical libraries. According to the method, at least two different chemical libraries are provided, with each library comprising a plurality of solid supports onto which at least two building blocks are coupled. Further, the solid supports of each library have a unique physical characteristic common to the library.

The two libraries are combined together to form a combined library, and the combined library is tested for positive outcomes. If any positive outcomes are observed, the library or libraries to which those solid supports belong are identified based on the physical characteristic of the solid supports.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1A is a schematic diagram of four groups of constructs which differ in size according to the invention.

Fig. 1B illustrates four groups of constructs which differ in density according to the invention.

Fig. 1C illustrates four groups of constructs, at least some of which differ in density, shape, and size according to the invention.

Fig. 2A is a schematic diagram of an exemplary construct according to the invention.

Fig. 2B is a schematic diagram of an alternative construct according to the invention.

Fig. 3 is a flow chart of an exemplary method for evaluating a chemical library according to the invention.

Fig. 4 is a schematic diagram of a process for producing a chemical library according to the invention.

Fig. 4A is an enlarged view of a discrete well of Fig. 4 taken along lines A-A.

Fig. 4B is an enlarged view of a reaction vessel of Fig. 4 taken along line B-B.

Fig. 5 is a schematic diagram illustrating the combination and subsequent evaluation of two or more different libraries according to the invention.

DETAILED DESCRIPTION OF THE SPECIFIC EMBODIMENTS

A "construct" as used herein, is a covalently bonded entity comprising, in any combination, some type of solid support, one or more linking components, one or more ligands, and optionally one or more ligand coding components.

A "ligand coding component" is a component which may be linked to a solid support and which contains information about at least one of the chemicals used to construct a ligand which is also linked to the solid support.

A "ligand" is a chemical reaction product of interest. A ligand can be part of a larger construct, where the ultimate goal will be to identify and/or cleave the ligand apart from the rest of the construct.

A "linking component" is a covalent bond or a molecular moiety that is suitable for linking two portions of a construct together.

A "solid support" is one or more materials upon which combinatorial chemistry synthesis can be performed, including beads, solid surfaces, solid substrates, particles, pellets, discs, capillaries, hollow fibers, needles, solid fibers, cellulose beads, pore glass beads, silica gels, polystyrene beads optionally crosslinked with divinylbenzene, grafted copoly beads, polyacrylamide beads, latex beads, dimethylacrylamide beads, optionally cross-linked N, N'-bis-acryloyl ethylene diamine, glass particles coated with a hydrophobic polymer, fullerenes and soluble supports, such as low molecular weight, noncrosslinked polystyrene.

The invention provides exemplary constructs having different physical characteristics which allows the constructs to be separated into different groups. The physical characteristics by which the groups may be separated facilitate the identification of a particular feature or aspect of the constructs within a given group. For instance, the common physical characteristics may be employed to identify the process by which the group is testable when screening the ligands. As another example, the common physical characteristic of a group may be used to identify a particular building block used in a synthesis process. As yet another example, the common physical characteristic may be employed to identify a particular library to which the construct belongs after two or more libraries have been combined.

The constructs of the invention may be constructed to have a wide variety of physical characteristics which allow the constructs to be separated into groups having at least one common physical characteristic. For example, physical characteristics which may be employed include size, density, geometry, color, magnetization, charge, refractive index, and the like. Conveniently, the physical characteristics may be categorized into types. For example, one type may be size and another type may be density. The invention may utilize differences within each type or across different types. For example, constructs may be constructed to have various sizes so that the constructs may be separated into the different groups based on their size. As another example, some of the constructs may be differently sized while other constructs may have a different geometry. Hence, a variety of combinations of physical characteristics may be provided based on differences within a given type and/or across various types.

Examples of different physical characteristics which may be utilized with the invention are illustrated in Figs. 1A-1C. In Fig. 1A, the solid supports are grouped into four groups, with each group having a different size. A variety of techniques may then be employed to separate the constructs into different groups. For example, different size sieves may be employed to filter the different size constructs. As another alternative, the constructs may be agitated so that the larger size constructs rise to the top. A bead picking apparatus, such as the one described in U.S. Patent Application Serial No. 09/240,758, filed January 29, 1999, the complete disclosure of which is herein incorporated by reference, may be utilized to remove the largest constructs. The constructs may then again be agitated and the process repeated for each of the groups. Other possible separation techniques include the use of magnets, fluorescence activated cells sorters, and other separation techniques known in the art.

An alternative scheme for separating constructs is illustrated in Fig. 1B. According to this scheme, each group of constructs has a solid support with a different density as represented by reference symbols ρ_1-ρ_4. To separate the constructs into groups, the constructs may be placed into a solution having a given density such that the group with the lowest density rises to the top of the solution.

These constructs may then be skimmed from the solution. The density of the solution is then increased until the group with the next largest density rises to the top of the solution. This process is then repeated until all the groups have been separated.

Fig. 1C illustrates another alternative for separating the constructs into different groups. In Fig. 1C, the constructs are categorized into different types. For example, groups 1 and 2 are classified by density, group 3 is classified by shape, and group 4 is classified by size. Further, the constructs within groups 1 and 2 differ within the same type. More specifically, group 1 has a density that is different than group 2. A variety of techniques may then be employed to separate the constructs into their respective groups. For example, an optical detector may be employed to determine differences in size and shape. Differences in density may be detected using different density of solutions as previously described. Agitation techniques may also be employed as previously described.

One advantage of the categorizing the solid supports into groups is that each group may be tested utilizing a different assay. In this way, one library may be produced which may be utilized with a variety of assays so that multiple libraries do not need to be constructed. This is best accomplished by assigning a physical characteristic to each group which is representative of the manner in which the linking components of the construct are assembled onto the solid support. To illustrate this principle, a typical construct 10 is shown schematically in Fig. 2A. Construct 10 includes a solid support 12 to which is coupled a linking component 14, a ligand coding component 16 and a ligand component 18. Although shown with only one linking component 14, it will be appreciated that other numbers and arrangements of linking components may be provided. For example, a linking component may be provided between ligand coding component 16 and ligand component 18. Such a construct is described in, for example, PCT International Application No. PCT/US97/05701, the complete disclosure of which is herein incorporated by reference. Another example of a construct 11 is shown in Fig. 2B and includes a solid support 12' and a pair of linking components 13 which are used to attach a ligand coding component 15 and a ligand 17. Such a construct is described in, for example,

U.S. Patent No. 5,770,358, the complete disclosure of which is herein incorporated by reference. Further, it will be appreciated that other types of constructs exist which may be utilized with the invention. For convenience of discussion, reference will be made hereinafter to construct 10.

Depending on the manner of assembly of constructs 10, and in particular, depending on the number, type and arrangement of the linking components, a different assay will need to be employed in order to screen the ligand component 18 following synthesis. For example, direct binding assays, lawn assays, solution assays, and the like all employ different types and/or arrangements of linking components as described generally in Daniolos, A. et al. *Pigment Cells Res.*, 3, 38-43 (1990); Jayawickreme, C. K., *Proc. Natl. Acad. Sci.* 91, 1614-1618; and Lam, Kit S., et al., "The 'One-Bead-One-Compound' Combinatorial Library Method", *Chem. Rev*, 1997, 97, 411-448, previously incorporated by reference. With lawn assays, synthesized beads in an agarose solution are typically poured onto plates containing cells, such as melanophore cells. After the agarose solidifies, the plates are exposed to UV light and scanned. Individual beads above responding areas may then be identified using a stereo microscope and removed. With direct binding assays, a bound target is detected either by direct visualization, e.g. a color target, or indirectly by using a reporter group such as an enzyme, a radionuclide, a fluorescent probe, or a color dye covalently attached to a target. For solutions assays, the ligands are cleaved from the solid supports into solution phase where biological assays can take plate. Such assays can include, for example, competitive receptor binding assays with radiolabeled ligands, various enzymatic assays, cell-based signal transduction assays, antibacterial assays, antiviral assays, and anticancer assays.

Typically, the linking and ligand coding components are attached to solid support 12 prior to a synthesis process. In this way, solid support 12 may be provided with a unique physical characteristic which may be used to identify the manner of attachment of the linking components. Once the solid support has been provided with the appropriate ligand coding component and linking component, the synthesis process proceeds to synthesize ligand component 18 to the solid support.

As described in greater detail hereinafter, it is preferred to synthesize the same set of ligand components to each group of solid support so that each group may be independently evaluated.

Referring now to Fig. 3, an exemplary method for processing the constructs will be described. As shown in step 20, multiple types of constructs which each have the same set of ligands is produced in a manner similar to that just described. In step 22, the constructs are physically separated into groups based on the types, i.e., based on the common physical characteristic that is unique to the group. Once the constructs have been physically separated, an assay is selected for each of the groups. The type of assay may be determined based on the physical characteristic that is common to the group as shown in step 24. In step 26, the selected assays are performed on each group of constructs to screen the ligands. Optionally, as shown in step 27, the constructs which produce positive results may be decoded to identify the ligand.

Referring now to Fig. 4, one exemplary way to construct a chemical library which has groups of constructs that are defined by different physical characteristics will be described. However, as previously described, it will be appreciated that the separating techniques of the invention may be used with a wide variety of constructs. The process of Fig. 4 is somewhat related to the techniques described in PCT International Application No. PCT/US97/05701, previously incorporated by reference, and in H. Mario Geysen, et al., Isotope or Mass Encoding of Combinatorial Libraries, *Chem. & Biol.* Vol. III, No. 8, pp. 679-688, August 1996, previously incorporated by reference. The process shown in Fig. 4 employs the use of a plate 28 having a plurality of wells 30. As shown, wells 30 are arranged in ten rows and ten columns to form a total of 100 wells. As best shown in Fig. 4A, a plurality of solid supports 32 are placed within each of the wells. Each of solid supports 32 preferably already includes one or more linking components and one or more ligand coding components. The manner of attachment of the linking components is identified by a physical characteristic of the solid support. As shown in Fig. 4A, well 30 includes solid supports 32 having four different densities as identified by reference

numerals ρ_1-ρ_4. Another group of solid supports has a size which is significantly larger than the other solid supports.

The size of solid supports 32 may vary depending on the particular application, and may range in size from about 1 μm to about 500 μm. Each well 30 preferably includes enough solid supports from each group to ensure that a complete set of ligands is produced on each of the groups.

Referring back to Fig. 4, each column of wells 30 is referenced by a reference numeral A_1-A_{10}, and each of the ten rows is identified by a reference numeral B_1-B_{10}. These reference numerals are provided schematically to show the particular chemicals that are introduced into each of the wells. For example, in the first well, each of the solid supports will receive A_1 and B_1 as the first two building blocks. In practice, a table will preferably be maintained indicating which chemicals are provided into each of the wells.

After the first two building blocks have been synthesized onto the solid supports, the solid supports are transferred to a pool 34 where they are thoroughly mixed. Following mixing, the solid supports within pool 34 are generally equally distributed into ten reaction vessels 36. Each of reaction vessels 36 is schematically marked with a reference numeral C_1 through C_{10}. These reference numerals indicate the third building block which is added to the associated reaction vessel 36. As shown in Fig. 4B, because the number of reaction vessels 36 is one-tenth the number of wells 30, each reaction vessel will receive approximately ten times the number of solid supports 32. Although shown with a ten by ten starting matrix and a one by ten ending matrix, it will be appreciated that a variety of other sized matrices may be employed. For example, the ending matrix may also be a ten by ten matrix.

Following synthesis of the third building block onto each of the solid supports, the solid supports are ready to be screened to determine any positive results. The type of screening to be performed will depend upon which group the construct belongs. Hence, prior to screening the solid supports within each of reaction vessels 36, the solid supports will be physically separated into groups based on the common physical characteristic of each group. When separating solid supports 32 into their

respective groups, the association of solid supports 32 relative to their reaction vessel 36 will be maintained so that the last building block is still identifiable.

One exemplary way to separate solid supports 32 into their different categories is first to agitate reaction vessels 36 and then utilize a bead picker to remove the larger size solid supports which will rise to the top of the remaining constructs. A solution may then be introduced into each of reaction vessels 36 to cause the least dense constructs to rise to the top of the fluid. These may be skimmed from the top and the density of the solution increased to allow the next of constructs to rise to the top. This process is repeated until all of the constructs are separated into groups.

Each of the groups may then be screened using assays that are suitable for the particular group. If a positive result is observed, the ligand coding component on the solid support may be used to identify the first two building blocks, with the third building block being determined based upon the reaction vessel 36 from which it was removed. In this way, the ligand may easily be identified using techniques known in the art.

Another application of the invention is the ability to combine two or more different libraries to make the next step in a process more efficient, while still providing the ability to identify the libraries from which any given construct originated. For example, two or more libraries may be combined prior to screening to make the screening process more efficient as illustrated in Fig. 5.

The process begins by providing two or more different libraries, with libraries A and N being shown for convenience of illustration. The manner in which the libraries differ may greatly vary. For example, the libraries may vary in that all of the building blocks and/or chemistries in one library are different from another library. As another example, the libraries may differ in that they were created at different times. As yet another example, the ligand coding assignments may differ between the libraries. As still another example, the libraries may differ except for common subsets of ligands within the libraries.

As shown in step 50, all of the libraries are combined and mixed. As shown in step 52, the entire library is then screened for positive outcomes. If one or more positive outcomes are observed, the physical characteristics of the positively tested constructs are evaluated to determine the library from which the constructs originated as shown in step 54. That particular library may then be individually tested. In this way, one initial screening may be performed with multiple libraries to reduce the time and effort employed to screen large quantities of constructs.

The invention has now been described in detail for purposes of clarity of understanding. However, it will be appreciated that certain changes and modifications may be practiced within the scope of the dependent claims.

WHAT IS CLAIMED IS:

1. A Chemical Library comprising:

a plurality of constructs which are separable into physically distinct groups where the constructs in each group have at least one common physical characteristic which is physically distinct from the physical characteristics of the constructs in all other groups, and wherein the common physical characteristic of each group is representative of the process by which the group is testable

2. A library as in claim 1, wherein the physical characteristics of the constructs are selected from a group consisting of size, density, geometry, color, magnetization, charge, and refractive index .

3. A library as in claim 1, wherein the physical characteristics are classifiable into categories, and wherein the category of at least one of the groups is different from the other groups.

4. A library as in claim 3, wherein one of the categories is size and another one of the categories is density.

5. A library as in claim 1, wherein each construct comprises a solid support to which are attached multiple components, including a ligand component, at least one linking component and at least one ligand coding component.

6. A library as in claim 5, wherein the constructs of each group have linking components which have been assembled in essentially the same manner.

7. A library as in claim 6, wherein the manner of assembly of the linking components of each group is unique to each group.

8. A library as in claim 5, wherein the ligand component is composed of at least two building blocks, and wherein each ligand code component is readable to determine one or more of the building blocks on each solid support.

9. A system of solid supports, comprising:

a plurality of solid supports;

a chemical compound comprising at least two building blocks synthesized to each solid support;

wherein the solid supports are separable into physically distinct groups where the solid supports in each group have at least one common physical characteristic which is physically distinct from the physical characteristics of the solid supports in all other groups, and wherein the common physical characteristic of each group are representative of the process by which the group is testable.

10. A system as in claim 9, wherein the physical characteristics of the solid supports are selected from a group consisting of size, geometry, density, color, magnetization, charge, and refractive index.

11. A system as in claim 9, wherein the physical characteristics are classifiable into categories, and wherein the category of one of the groups is different from the category of the other groups.

12. A system as in claim 11, wherein one of the categories is size and the other category is density.

13. A system as in claim 9, further comprising at least one ligand code linked to each solid support and which is readable to identify at least one of the building blocks.

14. A system as in claim 13, wherein each chemical compound comprises a first, a second, and a third building block, and wherein each ligand code is readable to identify the first and the second building blocks.

15. A system as in claim 13, further comprising at least one linker to link the ligand code to the solid support.

16. A system as in claim 15, wherein the solid supports of each group have linkers which have been assembled in essentially the same manner.

17. A system as in claim 16, wherein the manner of assembly of the linkers of each group is unique to each group.

18. A method for producing a chemical library, the method comprising:

providing a plurality of solid support groups, wherein each group includes multiple solid supports which have at least one common physical characteristic which is different from the physical characteristics of the solid supports in the other groups;

attaching at least one linking component to each of the solid supports, with the manner of attachment of the linking components being unique to each group as compared to the other groups; and

synthesizing a ligand onto each solid support such that each group of solid supports receives the same set of ligands.

19. A method as in claim 18, wherein the common physical characteristic of each group is representative of a process by which the group is testable.

20. A method as in claim 19, wherein the processes by which the groups are testable are selected from a group of processes consisting of direct binding assays, lawn assays, and solution assays.

21. A method as in claim 18, further comprising selecting the physical characteristics from a group consisting of size, geometry, density, color, magnetization, charge, and refractive index .

22. A method as in claim 18, wherein the physical characteristics are classifiable into categories, and wherein the category of one of the groups is different from the category of the other groups.

23. A system as in claim 22, wherein one of the categories is size and the other category is density.

24. A method as in claim 18, further comprising, prior to the synthesizing step, placing multiple solid supports into physically discrete locations such that each location includes at least one solid support from each of the groups.

25. A method as in claim 24, wherein the synthesizing step comprises synthesizing two building blocks onto each solid support while the solid supports are at the discrete locations, and further comprising attaching at least one ligand coding component to the solid supports, wherein the ligand coding component is representative of the two building blocks.

26. A method as in claim 25, further comprising combining the solid supports following synthesis of the two building blocks, mixing the solid supports, and allocating the solid supports into a plurality of vessels.

27. A method as in claim 26, further comprising synthesizing a third building block onto each of the solid supports while within the vessels.

28. A method for evaluating a chemical library, comprising:

providing a plurality of constructs which are typed by at least one common physical characteristic;

separating the constructs into groups based on their type; and

performing a different assay on each group of constructs.

29. A method as in claim 28, wherein the physical characteristic is density, and wherein the separating step comprises sequentially placing the constructs within fluids having different densities and removing the constructs that rise to the top of each fluid.

30. A method as in claim 28, wherein at least one of the physical characteristics is size, and further comprising agitating the constructs to permit the larger sized constructs to rise to the top of the remaining constructs.

31. A method as in claim 28, wherein each construct comprises a plurality of components including a linking component, a ligand coding component and a ligand component.

32. A library as in claim 31, wherein the constructs of each group have linking components which have been assembled in essentially the same manner such that the common physical characteristic of each group is representative of the process by which the group is testable.

33. A library as in claim 32, wherein the manner of assembly of the linking components of each group is unique to each group.

34. A method as in claim 28, wherein each group of constructs contains essentially the same ligand components.

35. A method as in claim 28, wherein the assays are selected from a group of assays consisting of direct binding assays, lawn assays, and solution assays.

36. A method for processing a chemical library, comprising:

providing a plurality of constructs which are typed by at least one common physical characteristic, wherein each type includes the same set of ligands, separating the constructs into groups based on their type; and

performing a different assay on each group of constructs.

37. A method as in claim 36, wherein the physical characteristic is density, and wherein the separating step comprises sequentially placing the constructs

within fluids having different densities and removing the constructs that rise to the top of each fluid.

38. A method as in claim 36, wherein at least one of the physical characteristics is size, and further comprising agitating the constructs to permit the larger sized constructs to rise to the top of the remaining constructs.

39. A chemical library system, comprising:.

at least two chemical libraries, wherein each chemical library comprises a plurality of solid supports onto which at least two building blocks are coupled;

wherein the solid supports of each library have a unique physical characteristic common to the library which allows the library to which each solid support belongs to be identified.

40. A system as in claim 39, wherein the physical characteristics of the solid supports are selected from a group consisting of size, geometry, density, color, , magnetization, charge, and refractive index.

41. A method for evaluating two or more different chemical libraries, . the method comprising:

providing at least two different chemical libraries, wherein each library comprises a plurality of solid supports onto which at least two building blocks are coupled, wherein the solid supports of each library have a unique physical characteristic common to the library;

combining the two libraries together to form a combined library;

testing the combined library for positive outcomes; and

identifying which library or libraries any positive outcomes belong based on the physical characteristic.

42. A system as in claim 41, wherein the physical characteristics of the solid supports are selected from a group consisting of size, geometry, density, color, magnetization, charge, and refractive index.

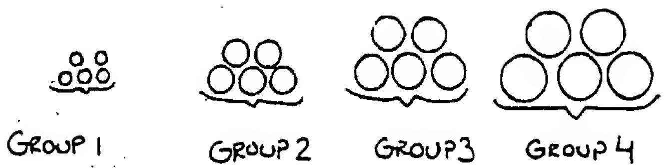


FIG. 1B

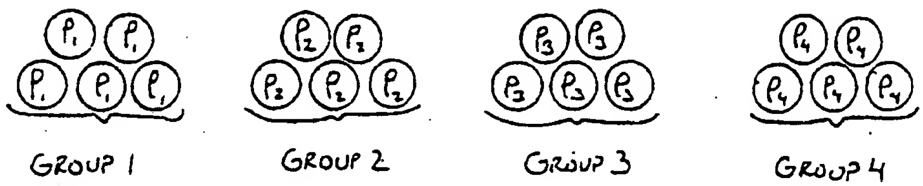
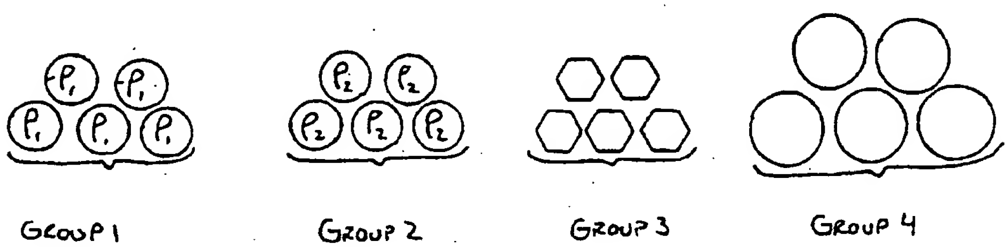


FIG. 1C



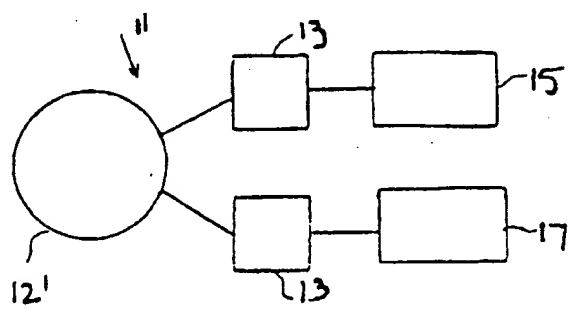


FIG. 2B

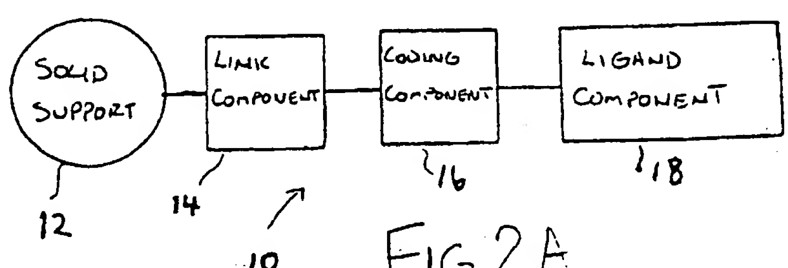


FIG. 2A

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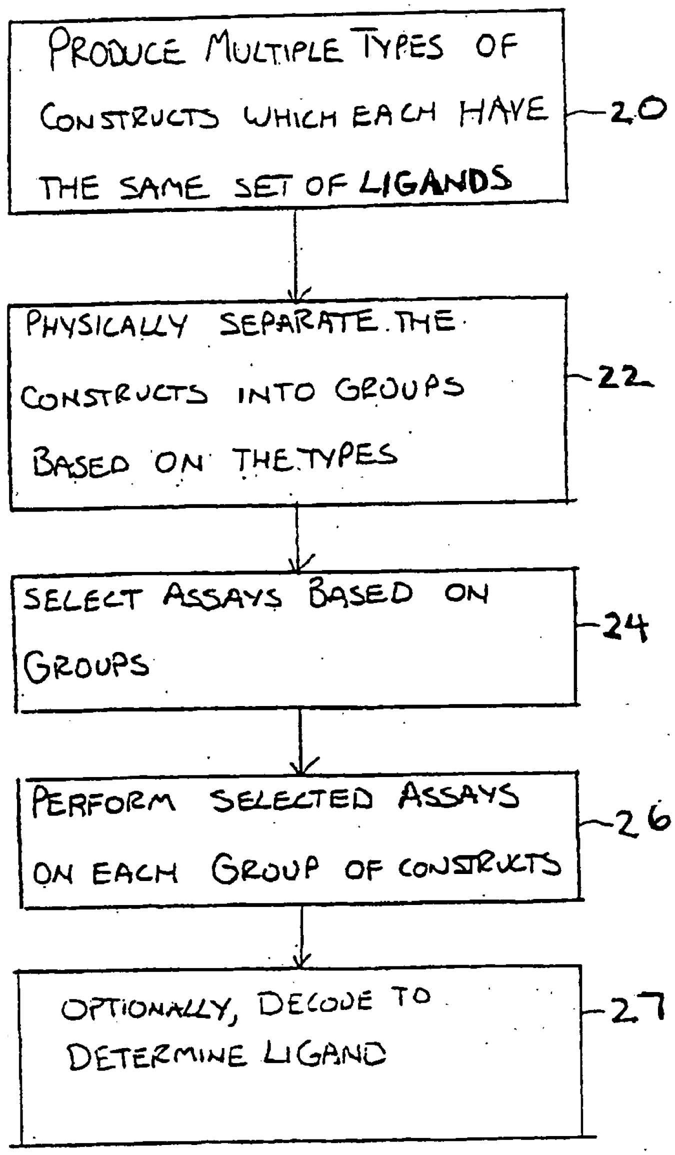
PRODUCE MULTIPLE TYPES OF CONSTRUCTS WHICH EACH HAVE THE SAME SET OF LIGANDS
20
PHYSICALLY SEPARATE THE CONSTRUCTS INTO GROUPS BASED ON THE TYPES
22
SELECT ASSAYS BASED ON GROUPS
24
PERFORM SELECTED ASSAYS ON EACH GROUP OF CONSTRUCTS
26
OPTIONALLY, DECODE TO DETERMINE LIGAND
27

FIG. 3

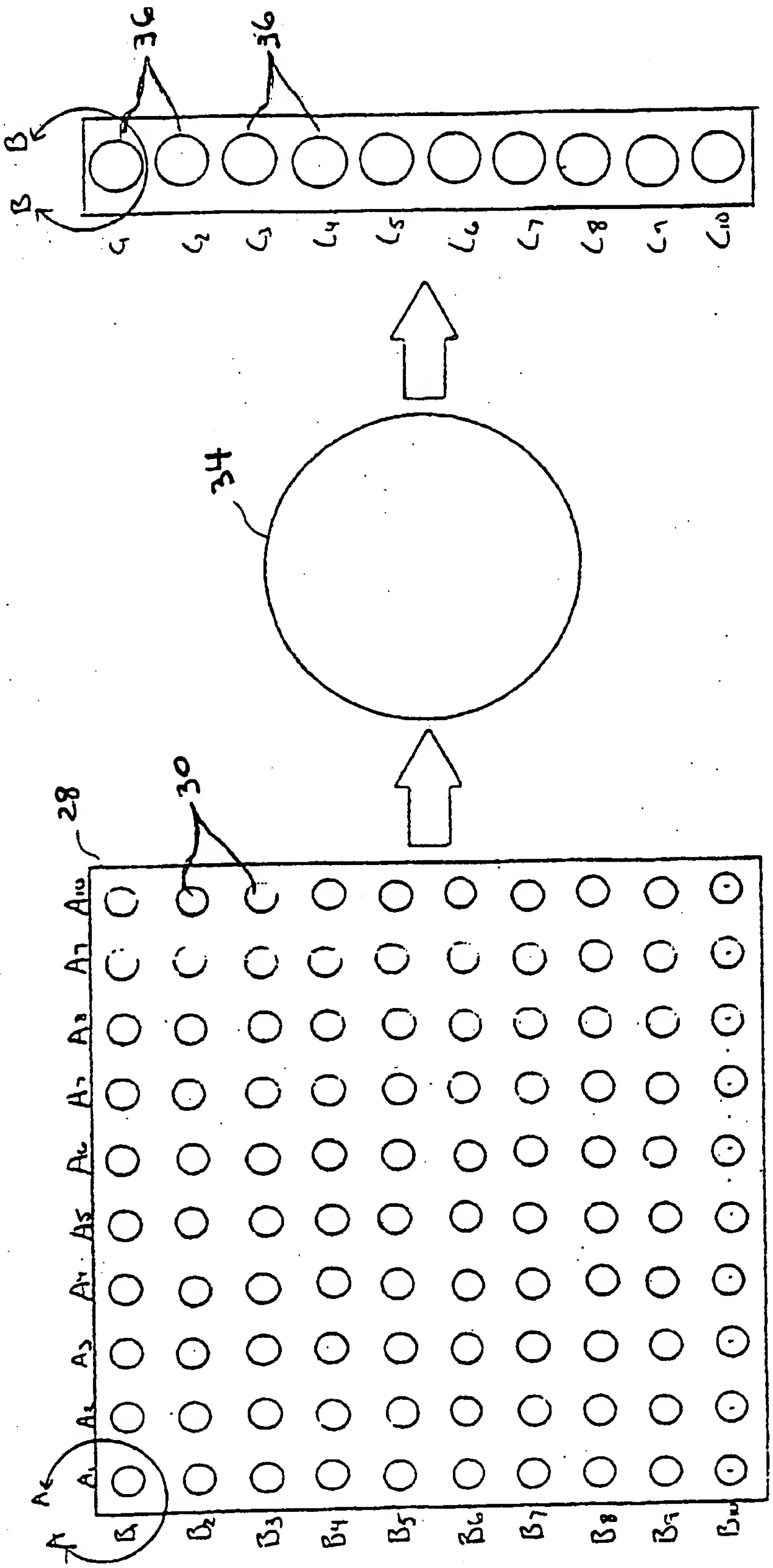

FIG. 4

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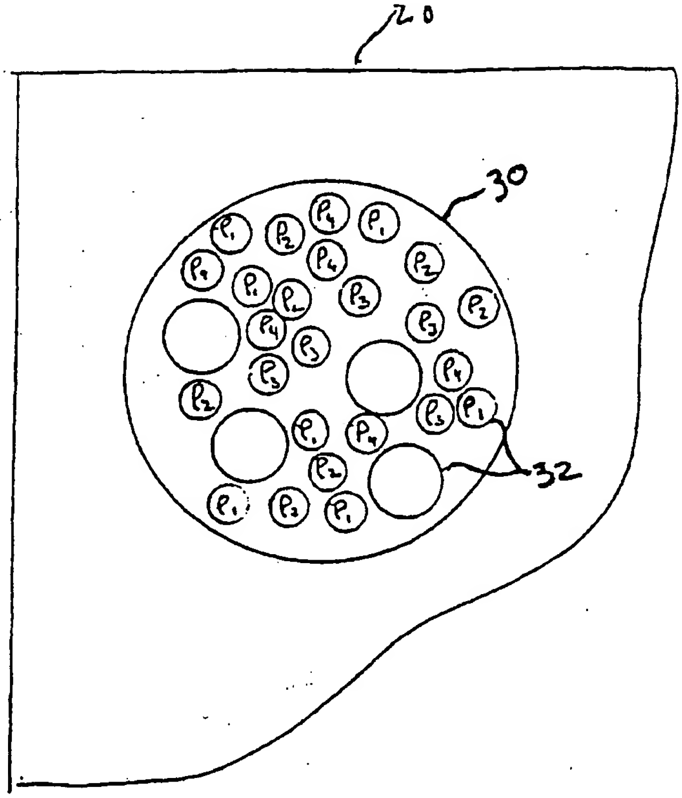


FIG. 4A

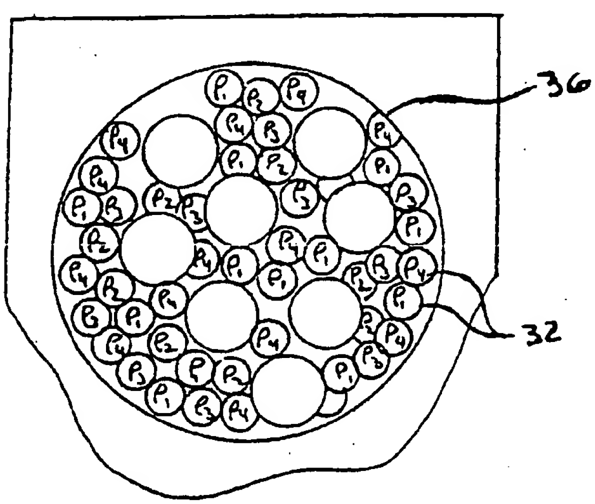
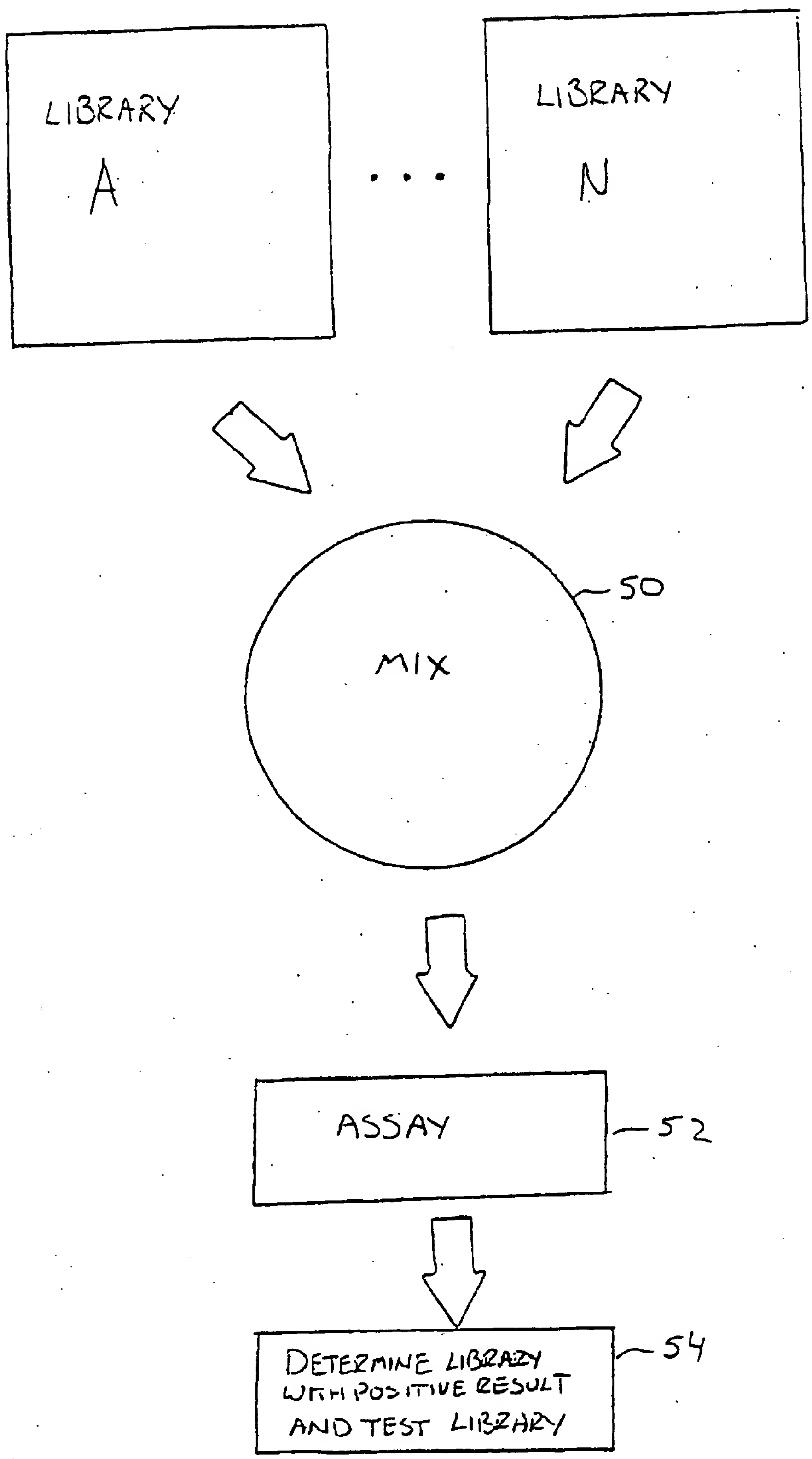


FIG. 4B

FIG. 5


LIBRARY
A
LIBRARY
N
MIX
50
ASSAY
52
DETERMINE LIBRARY
WITH POSITIVE RESULT
AND TEST LIBRARY
54

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/09093

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01J19/00 C07B61/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01J C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, INSPEC, COMPENDEX, WPI Data, PAJ

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A	page 7, line 15 -page 8, line 12; figures 2A,3 page 14, line 17 - line 23 page 17, line 13 - line 27 ---	28-38
X	EGNER B J ET AL: "TAGGING IN COMBINATORIAL CHEMISTRY: THE USE OF COLOURED AND FLUORESCENT BEADS" CHEMICAL COMMUNICATIONS,GB,ROYAL SOCIETY OF CHEMISTRY, 1997, pages 735-736, XP000876998 ISSN: 1359-7345	1-3,5,6, 9-11, 39-42
A	the whole document --- -/--	18-27

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 August 2000	07/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Veefkind, V

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In. ational Application No
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International Application No
PCT/US 00/09093

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	K S LAM ET AL: "The One-Bead-One-Compound Combinatorial Library Method" CHEMICAL REVIEWS, US, AMERICAN CHEMICAL SOCIETY. EASTON, vol. 97, no. 2, March 1997 (1997-03), pages 411-448, XP002097485 ISSN: 0009-2665 cited in the application page 428, column 2 -page 432, column 1; figure 36 -----	18-38

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Information on patent family members

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